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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,231	05/15/2002	Hagen Thielecke	5686	2577

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EXAMINER	
JUNG, UNSU	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 11/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,231	THIELECKE ET AL.	
	Examiner	Art Unit	
	Unsu Jung	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicants' amendments to the specification in the reply filed on September 19, 2005 have been acknowledged and entered.

2. Applicants' amendments to the claims 1-6 in the reply filed on September 19, 2005 have been acknowledged and entered.

3. Applicants' amendment to cancel claims 7-10 in the reply filed on September 19, 2005 have been acknowledged and entered.

4. Claims 1-6 are pending.

Specification

5. In view of amendments to the specification in the reply filed on September 19, 2005, the objections to the specification are withdrawn.

Claim Objections Withdrawn

6. In view of amendments to the claims 1-6 in the reply filed on September 19, 2005, the objections to the claims are withdrawn.

Rejections Withdrawn

7. Applicant's arguments, see pp10-11, filed on September 19, 2005, with respect to the rejection of claims 1-6 under 35 U.S.C. 112, second paragraph, have been fully considered and are persuasive. The rejection of claims 1-6 under 35 U.S.C. 112, second paragraph has been withdrawn.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Damay (Rheology of Blood Cells in Sickle Cell Disease", Thesis in M.S., University of Florida, 1997) in view of Frank et al. (U.S. Patent No. 5,686,309, 1997), Schwan et al. (The Review of Scientific Instruments, Vol. 39, pp481-485, 1968), and Kyle et al. (Biophysical Journal, May 1999, Vol. 76, pp2640-2648).

Damay teaches a method of modeling cell deformation by introducing a cell into a tube having an inner diameter, which is step-like and smaller than the diameter of the cell (p59, lines 16-19 and p60, Figure 5.1(a)). A fluorescent method is used to model the leukocyte rheological behavior. Damay also discloses a method of making a conically shaped tube with a longitudinal axis by pulling a heated glass capillary tube, which is an electrically insulating material (p23, lines 15-17). However, Damay fails to teach a method of characterizing spheroid deformation by using bioelectric impedance measurement, including two pairs of electrodes.

Frank et al. teaches a method of characterizing cell deformation to measure bioelectric impedance by using an apparatus which comprises a tube (flow cell) having

a constricted region with two electrodes, which are connected to a current source (current source) and a voltage source (resistance detector), inserted in the tube to measure impedance (resistance) of individual cells deformed by means of hydrodynamic force (Sheet 1 of 7, Figure 1 and column 10,lines 59-60). Such an electrical measurement would provide an improved application that has the ability to quickly and accurately determine individual cell concentration at a lower cost with a simpler instrument than the optical system (column 3, line 67 to column 4, line 5). However, Frank et al. uses two electrode technique and fails to teach the use of four electrode technique to measure impedance of a deformed cell.

Schwan et al. teaches the use of bioelectric impedance techniques such as four electrode technique, in which two inner electrodes are connected to a voltage meter and two outer electrodes are connected to a current source to measure impedance of a biological sample (p482, Figure 1) by measuring voltage and frequency (impedance spectrum/spectrogram, Abstract). Schwan et al. further teaches that for materials of relatively high conductivity, such as physiologic fluids, cell suspensions and tissues, electrode polarization cause the approximation to the voltage across the sample to weaken and at sufficiently low frequencies to fail (p487, column 1, Introduction, lines 6-10). Four electrode measurement techniques have been used to eliminate the problem of electrode polarization associated with two-electrode apparatus by providing a second pair of electrodes, non-current-carrying, with which to measure the voltage across the sample (p481, column 1, Introduction, lines 14-17). However, Schwan et al. fails to specifically disclose measurement of spheroids.

Kyle et al. teaches a method of using electrical impedance spectroscopy to characterize cell environment of multilayered cell cultures (MCCs), a culture system in which cells are grown on a permeable support membrane to form a thick disc of cells with tumor-like properties (*Abstract*). Over the past 20 years, three-dimensional tissue cultures have been increasingly used to model the extravascular compartment of solid tumors (p2640, left column, *Introduction*, lines 1-3). Usually, three-dimensional cultures have been grown in the form of spheroids (p2640, left column, *Introduction*, lines 3-4). Spheroidal and MCCs mimic the tumor environment better than monolayer cell cultures because their three-dimensional structure permits increased cell-to-cell interaction (p2640, left column, *Introduction*, lines 9-12). Because the extracellular space may be the primary route of penetration into tumor tissue for many therapeutic drugs, it is critical that this factor be well characterized for any in vitro tumor model (p2640, right column, line 34-p2641, left column, line 2).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include in the device of Damay, with an electrode system as taught by Frank et al. in order to determine deformation characteristics of cells by measuring bioelectric impedance of the cell under deformation quickly and accurately at a lower cost. Furthermore, it would have been obvious to one of ordinary skill in the art to employ in the device of Damay with a four electrode technique as taught by Schwan et al. in order to eliminate the problem of electrode polarization associated with a two electrode system to measure bioelectric impedance of a biological sample. Finally, it would have been obvious to one of ordinary skill in the art to include in the device of

Damay et al. with spheroids, which mimic the tumor environment, as taught by Kyle et al. in order to measure bioelectric impedance of spheroids to characterize cell environment for in vitro tumor models such as spheroids as extracellular space may be the primary route of penetration into tumor tissue for many therapeutic drugs.

With respect to claim 4, the inner diameter of Damay is dependent on the cell type because Damay teaches that the cell must flow through a constricted geometry to induce deformation of the cell in order to perform resistance measurement. Therefore, it would have been obvious to one of ordinary skill in the art to modify the inner diameter of Damay within a particular dimension depending on the type of cells. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 105 USPQ 233.

With respect to claim 6, Damay teaches a constricted region including part of the tube, which starts narrowing, a step, as well as the region of the tube with the smallest diameter along the longitudinal axis (Figure 5.1).

Response to Arguments

12. Applicant's arguments filed on September 19, 2005 have been fully considered but they are not persuasive.

In response to Applicants argument that the object to the instant invention is not to deform cells but to ensure that the spheroids are in mechanical contact over the entire circumference with the electrically insulating inner wall of the tube, so that no

electrical bypass occurs and the applied current always flows through the spheroid on p12, the object of the current invention is irrelevant as Damay teaches a tube having an inner diameter in a constricted region that is smaller than the diameter of cells.

Applicants argue on p13 that Damay does not disclose a constricted region of a tube, in which the inner diameter of the tube changes in steps along the longitudinal axes as claimed. However, Applicants further argues that Damay in fact shows an arrangement, in which a step is indicated for forming the constricted region in Figure 5.1. In the Figure 5.1 of Damay, the constricted region includes part of the tube, which starts narrowing, a step, as well as the region of the tube with the smallest diameter.

In response to Applicants argument that the device of Frank et al. does not have a constricted region with an inner diameter smaller than the diameter of the red blood cells to be examined, the Examiner agrees that Frank et al. fails to disclose a device, which has a constricted region with an inner diameter smaller than the diameter of the red blood cells to be examined. However, as stated in the Office Action filed on May 18, 2005, Frank et al. teaches a method of characterizing cell deformation by measuring bioelectric impedance and that the cell deformation was carried out by means of hydrodynamic force not mechanical. Damay, not Frank et al., teaches the mechanical deformation of the cell.

Applicants argue that Frank et al. fails to teach a method of measuring an impedance spectrum and therefore the measurement arrangement taught by Frank et al. does not produce an impedance spectrogram as claimed (pp13-14). This argument is not found persuasive because Frank et al. does teach a method of measuring

impedance (resistance) of individual cells deformed by means of hydrodynamic force (Figure 1 and column 10, lines 59-60).

Applicants' argument that Frank et al. teaches other means for measuring a cell deformation on p14 is irrelevant as Frank et al. teaches a method of measuring impedance (resistance) of individual cells deformed by means of hydrodynamic force (Figure 1 and column 10, lines 59-60).

In response to Applicants argument that Frank does not disclose any measurement arrangement for producing an impedance spectrum on p15, Schwan et al. teaches a method of four electrode technique, in which two inner electrodes are connected to a voltage meter and two outer electrodes are connected to a current source to measure impedance of a biological sample (p482, Figure 1) by measuring voltage and frequency (impedance spectrum, Abstract).

Applicants further argue on p15 that Schwan does not give any further motivation for a combination of Damay and Frank et al. This argument is not found persuasive as motivation for combining Damay and Frank et al. is discussed in the Office Action filed on May 18, 2005. As discussed above and in the Office Action filed on May 18, 2005, Schwan et al. teaches that for materials of relatively high conductivity, such as physiologic fluids, cell suspensions and tissues, electrode polarization cause the approximation to the voltage across the sample to weaken and at sufficiently low frequencies to fail (p487, column 1, Introduction, lines 6-10). Four electrode measurement techniques have been used to eliminate the problem of electrode polarization associated with two-electrode apparatus by providing a second pair of

electrodes, non-current-carrying, with which to measure the voltage across the sample (p481, column 1, Introduction, lines 14-17). Therefore, it would have been obvious to one of ordinary skill in the art to employ in the device of Damay with a four electrode technique as taught by Schwan et al. in order to eliminate the problem of electrode polarization associated with a two electrode system to measure bioelectric impedance of a biological sample.

In view of the responses to the arguments, Frank et al. and Schwan et al. make up for the shortcomings of Damay as set forth above as Frank et al. and Schwan et al. suggest motivation to modify teachings of Damay as discussed above. Accordingly, Damay in view of Frank et al. and Schwan et al. does render the claimed invention obvious under 35 U.S.C. 103(a) set forth in the Office Action filed on May 18, 2005.

Conclusion

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Unsu Jung whose telephone number is 571-272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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